PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	19.10.2005
Applicant's or agent's file reference PN0368-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NO2004/000287	28.09.2004	29.09.2003

Applicant
AMERSHAM HEALTH AS

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Cardenas, C Tel. +31 70 340-3370

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PN0368-PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/NO2004/000287	International filing date *(day/month/year)* 28.09.2004	Priority date *(day/month/year)* 29.09.2003
International Patent Classification (IPC) or national classification and IPC A61K49/00, A61K47/48		
Applicant AMERSHAM HEALTH AS		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.07.2005	19.10.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Gonzalez Ramon, N Telephone No. +31 70 340-

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NO2004/000287

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-29 as originally filed

   Claims, Numbers

   1-12 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-12 in part

because:

☒ the said international application, or the said claims Nos. 10-12 in relation to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-12 in part

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-12
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-12
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	10-12

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

10/573606
IAP20 Rec'd PCT/PTO 28 MAR 2006

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/NO2004/000287

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 10-12 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Method of diagnosis

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

In the present application, the International Searching Authority has restricted the search under the following objections under Articles 5 and 6 PCT:

Present claims 1-12 encompass a genus of compounds defined only by their function: "with affinity for an abnormally expressed biological target associated with CRC" (claims 1, 2); "reporter moiety detectable in optical imaging" (claim 3), "a contrast agent substrate" (claim 4), "target an abnormally expressed enzyme" (claim 4), "changes pharmacodynamic properties or pharmacokinetic properties upon a chemical modification from a contrast agent substrate to a contrast agent product upon a specific enzymatic transformation" (claim 4); "having affinity for target selected from COX-2, ... gastrin receptors" (claim 5) wherein the relationship between the structural features of the members of the genus and said function have not been defined.

In the absence of such a relationship either disclosed in the as-filed application or which would have been recognized based upon information readily available to one skilled in the art, the skilled artisan would not know how to make and use compounds that lack structural definition.

The fact that one could have assayed a compound of interest using the described assays does not overcome this defect since one would have no knowledge beforehand as to whether or not any given compound (other than those that might be particularly disclosed in an application) would fall within the scope of what is claimed. It would require undue experimentation (be an undue burden) to randomly screen undefined compounds for the claimed activity.

Furthermore present claim 6 relate to compounds defined by reference to vague characteristics or properties, namely " peptide", "peptoid moiety", "oligonucleotide", "oligosaccharide", "lipid related compound", "traditional organic drug-like small molecules"

The claim covers all compounds having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

Support is only to be found in the present application for the compounds specifically mentioned by chemical name in the examples and on description passages on pages 9, line 1- page 10, line 10; page 11, line 20- page 12, line 5 and page 14, line 25- page 15, line in connection to their use as optical imaging contrast agents. Consequently the search has been restricted to the subject matter for which this support has been found.

No opinion will be given in respect of subject-matter which is not covered by the search report (Rule 66.1(e) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

For the assessment of the present claims 10-12 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in a diagnostic method, but may allow, however, claims to a known compound for first use in a diagnostic method and the use of such a compound for the

manufacture of a medicament for a new diagnostic method.

The applicant's attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up.

The following documents (D) are referred to in this communication

D1: MARTEN K ET AL: GASTROENTEROLOGY, W.B.SAUNDERS COMPANY, PHILADELPHIA, US, vol. 122, no. 2, February 2002, pages 406-414, XP008044304

D2: WO 02/26776 A (NYCOMED IMAGING AS; CUTHBERTSON, ALAN; AMERSHAM HEALTH AS) 4 April 2002

D3: WEISSLEDER, R. ET AL, Nature Biotechnology, vol. 17, April 1999, pages 375-378, XP001164273

Novelty (Article 33 (2) PCT)

The subject-matter of present claims 1-12 is not novel in the sense of Article 33(2) PCT

D1 discloses the detection of dysplastic intestinal adenomas using cathepsin B sensing near infrared fluorescence (NIRF), containing Cy5.5 monofunctional dye in a conjugate with lys-lys cleavage site (see page 406, col. 1; page 408, col. 2; figure 1). Said probe is indicated to reduce the incidence of colorectal cancer (see discussion).
Therefore the subject matter of claims 1-12 is not novel over D1.

D2 discloses V-L-R imaging agent wherein R is a reporter for light imaging in the near infrared range, chromophores and fluorophores, L is a linker and V is a peptide vector having affinity for the integrin avb3 (see page 23, paragraph 5- page 24, paragraph 1; page 17, lines 1-2; page 6; paragraph 3-4) Indication for colorectal cancer is also encompassed (see page 3, line 4).
Consequently the subject matter of claims 1-4, 6-12 is not novel over D2.

Inventive step (Article 33 (3) PCT)

The subject matter of present claims 1-12 cannot be considered as involving an inventive step for the following reasons:

According to the applicant (see page 2, lines 19-31) the problem underlying the present application is the early detection of colorectal cancer.

The solution proposed is the use of optical imaging contrast agent with affinity for an abnormally expressed biological target associated with CRC.

Document D1, which can be considered the closest prior art for the assessment of inventive step of the present application, already addresses the early detection of colorectal cancer with the use of a cathepsin B sensing near infrared fluorescence imaging probe.
The detection of colonic adenomatous polyps as ultimately they lead to carcinoma formation has been shown to reduce the incidence of colorectal cancer (see page 406, col. 1, paragraph 2-col. 2, paragraph 1) is therefore encompassed under the diagnosis of CRC (colorectal carcinoma).

The difference between D1 and the subject matter of part of present claim 5 is the use of different alternative affinity targets than the cathepsin B protease.

Therefore the remaining problem can be formulated as the use of an alternative target associated with the colorectal cancer for the optical contrast detection of colorectal cancer.

Such solution cannot be considered as involving an inventive step but as an obvious result of routine practice in determining a suitable target can be easily determined by the skilled man in the field only relying on known properties of known compounds.

The skilled person would have been reinforced in his choice by the teaching of D3 where the in vivo imaging of tumours as colonic cancer with protease-activated near-infrared fluorescent probes is described and strategies to imaging other tumor-associated proteases as matrix metalloproteases (MMP) is also presented (see page 377, col. 2, paragraph 1)

Consequently an inventive step for the subject matter of present claims 1-12 cannot be acknowledged.

Furthermore the attention of the applicant is also drawn to the fact that all embodiments covered by the claims should satisfy the criteria of inventive step.

When the inventive step is solely based on the achievement of a technical effect, as the optical imaging contrast agent in the present case, substantially all embodiments of independent claim 1 should exhibit this effect.

However, it is evident that the number of optical agents encompassed under "with affinity for an abnormally expressed biological target associated with CRC" (claims 1, 2); "reporter moiety detectable in optical imaging" (claim 3), "a contrast agent substrate" (claim 4), "target an abnormally expressed enzyme" (claim 4), "changes pharmacodynamic properties or pharmacokinetic properties upon a chemical modification from a contrast agent substrate to a contrast agent product upon a specific enzymatic transformation" (claim 4); "having affinity for target selected from COX-2, ... gastrin receptors" (claim 5) is such that it is unlikely that all of them posses the therapeutic effect claimed.

Therefore, as part of the subject matter of claims 1-12 does not exhibit this particular technical effect in a credible manner, said subject matter cannot involve inventive step.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO2004/062568	29.07.2004	09.01.2004	09.01.2003
WO2005/003166	13.01.2005	07.07.2004	08.07.2003

The PCT application WO 2004/062568 published on 29.07.2004 claims the priority date of 09.01.2003.
This earlier application shows: V-L-R imaging agent wherein R is a reporter for light

imaging in the near infrared range, chromophores and fluorophores, L is a linker and V is a peptide vector having affinity for the angiotensin II receptor (see page 4). Exemplified for losartan as present example 6 (see examples 2, 7).

Thus, it would prejudicial to the novelty of the subject-matter of claims 1-8, 10-12 of the present application.

The PCT application WO 2005/003166 published on 13.01.2005 claims the priority date of 08.07.2003.
This earlier application shows: V-L-R optical imaging agent wherein R is fluorescein dye, L is a linker and V is a peptide vector having affinity for the integrin avb3 (see abstract, claims 12, 13; page 13-15). Indication for colorectal cancer is also encompassed (see page 2, line 25).

Thus, it would prejudicial to the novelty of the subject-matter of claims 1-12 of the present application.